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CONTRACEPTIVE AND PHARMACEUTICAL PACK THEREOF

It is known that gestagens and estrogens alone or in combination may be used for contraception. Characteristic thereof are the following types:

a) Combination preparations containing an estrogen and a gestagen, which are generally taken from the fifth day of a menstrual cycle for 20 or 21 days;

b) Sequential preparations, which include the intake of an estrogen starting approximately on the fifth day of the cycle and subsequently a combination of estrogen and gestagen. For this type, numerous variants have been suggested; and

c) Continuously taken gestagen preparations, so-called minipills, which include a daily intake, without interruption, of gestagen for a few days.

Disadvantages of the aforesaid preparations include, among other things, the intake of too high doses of estrogen, and the thereby caused side effects, such as gastrointestinal disorders, nausea, weight increase with formation of edema, risk of thromboembolic symptoms, deviation from the normal physiological cycle or ovulation process, intermediate bleedings, cycle variations, etc.

It has now been found that a reliable contraception may be realized by initially administering a gestagen during the first days of the female cycle, followed by a combination of a gestagen and an estrogen during the following days, and by eliminating gestagen and estrogen during the last days of the female cycle.

This allows to reduce the strain on the female organism by steroids, in particular, the estrogen. Furthermore, it allows to

realize a better control of the cycle as well as a reduction of the intermediate bleeding rate.

It is therefore the object of the invention to provide a method of contraception, which is characterized by initially administering a gestagen during the first days of the female cycle, a combination of a gestagen and an estrogen during the following days, and by eliminating gestagen and estrogen during the last days of the female cycle.

Considered as day 1 is the day after the menstrual bleeding of a reproductive female. "First days" are understood to be a period of 5 to 8 days, preferably 7 days, whereas the following days comprise a period of 12 to 16 days, preferably 14 days. The "last days", which are kept free from the intake of gestagen and estrogen for adaptation to the normal cycle of a woman of about 28 days, apply to a period of 5 to 8 days, preferably 7 days. During this last phase, one may administer just as well placebos or other gestagenfree or estrogenfree ingredients, without thereby affecting the reliability of the method.

The present invention further relates to sequential contraceptives, which contain a gestagen in the first stage, as well as a combination of a gestagen and an estrogen in the second stage besides carrier substances, taste corrigents and/or fillers that are typically used by the galenic pharmacy.

In accordance with the invention, a suitable gestagen component includes all gestagen-effective substances. Preferably, the gestagen in use ought to be given in such doses that the quantity of gestagen employed in accordance with the invention during the first days (first stage) is equal to that which corresponds to the daily intake of 0.300 to 2.000 mg, preferably 0.500 to 0.700 mg of norethisterone acetate. The quantity of gestagen used in accordance with the invention during the following days of the second stage ought to be equal to that corresponding to the daily intake of 0.300 to 2.000 mg, preferably 0.500 to 0.700 mg norethisterone acetate. Suitable for use as a gestagen component are, among other things,

progesterone and its derivatives, such as, for example, 17-hydroxyprogesterone ester and 19-nor-17-hydroxyprogesterone ester, 17α-ethinyl testosterone, as well as 17α-ethinyl-19-nortestosterone, and their derivatives. Derivatives are understood to be compounds which are formed by the introduction of a double bond or double bonds, by substitution, or production of functional derivatives, such as, for example, esters, ethers, ketals, etc.

Double bonds may be present, among other things, in 1(2)-, 6(7)-, and/or 16(17)-position. Among others, such substituents may be considered as halogens, in particular, fluorine, chlorine, and bromine atoms, low alkyls, in particular the methyl groups, alkenyl, alkynyl, in particular the ethinyl group, and/or the hydroxy group, which may be in 1(2)-, 6(7)-, 15(16)- and/or 16(17)-position. Such esters may be considered as the esters of acids, which are normally employed in the chemistry of steroids for the esterification of steroid alcohols. Some examples to name are alkane carboxylic acids, in particular, alkane carboxylic acids with 1 to 16 carbon atoms. Ethers include, for example, alkyl- and tetrahydropyranyl ethers. Ketals are, for example, those of the ethanediol or those of the propanediol.

Gestagens include, for example: norethisterone acetate, D- and DL-norgestrel, cyproterone acetate, ethynodiol acetate, lynestrenol, chlormadinone acetate, etc.

Preferred gestagens are 17α-ethinyl-19-nortestosterone acetate, D-norgestrel, and cyproterone acetate.

An estrogen component suited for the contraceptive method of the present invention includes common estrogen. Preferably, the estrogen in use ought to be administered in such doses that the estrogen quantity used in accordance with the invention during the following days (of the second stage) is equal to that corresponding to the daily intake of 0.020 to 0.050 mg of 17α-ethinyl estradiol. Suitable for use as an estrogen component are, among others, also 17α-ethinyl estradiol esters or -ethers, for example mestranol. Also the natural estrogens may be

considered, for example, estrone, estradiol, or estriol, and their esters, such as estradiol valerate. Preferred is 17α-ethinyl estradiol.

The gestagen as used in accordance with the invention in the first and the second stage may be the same as well as different. If different gestagens are used in the first and second stages, the method has, aside from the aforesaid advantages, the further advantage of reducing or eliminating the side effects of a certain gestagen, in that this gestagen is taken only during the one stage, whereas in the other stage a different gestagen is taken, which exhibits a competitive behavior with respect to the side effects.

Thus, for example, one may use in the first stage a gestagen which is derived from testosterone or 19-nortestosterone, and has in the 17α-position a substituted hydrocarbon residue. In general, these (19-nor-)testosterone derivatives exhibit a small androgenic side effect. In the other stage, a gestagen may be used, which is derived from progesterone and does not exhibit the androgenic side effect inherent to the testosterone or 19-nortestosterone compounds. Considered as especially advantageous gestagens are such progesterone derivatives, which possess an antiandrogenic side effect besides their gestagenic action.

If different gestagens are used in the first and the second stage, a preferred embodiment uses in the first stage a testosterone or 19-nortestosterone derivative, and in the second stage a progesterone derivative in combination with an estrogen.

Preferably, the estrogenic or gestagenic active ingredient components are taken orally. To this end, the active ingredients are processed with additives, carrier substances and/or taste corrigents that are common in the galenic pharmacy, by methods known per se, to standard forms of application. Considered for the preferred, oral application are in particular tablets, dragées, capsules, pills, suspensions, or solutions. For the preferred application, the contraceptives of the present invention are suitably combined to a pharmaceutical pack, which

accommodates in sequential form the formulation representing the daily dosage.

It is therefore a further object of the invention to provide pharmaceutical packs, which are characterized in that they contain the contraceptives in dosage units in an adapted, certain sequence, the sequence corresponding to the stages of the daily intake.

Among other things, the pharmaceutical pack may be realized in the form of a deep-draw [literal] pack containing, for example, 7 dragées of the first stage (gestagen), 14 dragées of the second stage (combination of gestagen and estrogen), and 7 placebos, which may be taken daily, namely over 28 days. A 21-tablet pack would be realized without the seven placebos. Modification with respect to the daily dosage, the realization of the form of application, the form of the pack, etc. are well-known to the person skilled in the art.

The following examples serve for a better illustration of the invention:

Example 1 (Composition per dragée)

1st Stage	0.600 mg	norethisterone acetate
(7 dragées, white	32.650 mg	lactose
colored)	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
2nd Stage	0.050 mg	17α-ethinyl estradiol
(14 dragées	0.600 mg	norethisterone acetate
red colored)	32.600 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1,650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
3rd Stage	33.250 mg	lactose
(7 dragées	18.000 mg	corn starch
orange colored)	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.

Example 2 (Composition per dragée)

1st Stage	0.030 mg	D-norgestrel
(7 dragées)	33.220 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
2nd Stage	0.050 mg	17α-ethinyl estradiol
(14 dragées)	0.030 mg	D-norgestrel
	33.170 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
3rd Stage	33.250 mg	lactose
(7 dragées)	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.

Example 3 (Composition per dragée)

1st Stage	0.500 mg	cyproterone acetate
(7 dragées)	32.750 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
2nd Stage	0.050 mg	17α-ethinyl estradiol
(14 dragées)	0.500 mg	cyproterone acetate
	32.700 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
3rd Stage	33.250 mg	lactose
(7 dragées)	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.

Example 4 (Composition per dragée)

1st Stage	0.300 mg	norethisterone
(7 dragées)	32.950 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
2nd Stage	0.050 mg	17α-ethinyl estradiol
(14 dragées)	0.300 mg	norethisterone
	32.900 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
3rd Stage	33.250 mg	lactose
(7 dragées)	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.

Example 5 (Composition per dragée)

1st Stage	0.500 mg	ethynodiol acetate
(7 dragées)	32.750 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
2nd Stage	0.050 mg	17α-ethinyl estradiol
(14 dragées	0.500 mg	ethynodiol acetate
	32.700 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
3rd Stage	33.250 mg	lactose
(7 dragées)	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.

Example 6 (Composition per dragée)

1st Stage	0.500 mg	lynestrenol
(7 dragées)	32.750 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
2nd Stage	0.050 mg	17α-ethinyl estradiol
(14 dragées)	0.500 mg	lynestrenol
	32.700 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
3rd Stage	33.250 mg	lactose
(7 dragées)	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.

Example 7 (Composition per dragée)

1st Stage	0.500 mg	chlormadinone acetate
(7 dragées)	32.750 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
2nd Stage	0.050 mg	17α-ethinyl estradiol
(14 dragées)	0.500 mg	chlormadinone acetate
	32.700 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
3rd Stage	33.250 mg	lactose
(7 dragées)	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.

Example 8 (Composition per dragée)

1st Stage	0.600 mg	norethisterone acetate
(7 dragées)	32.650 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
2nd Stage	0.080 mg	mestranol
(14 dragées)	0.600 mg	norethisterone acetate
	32.750 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
3rd Stage	33.250 mg	lactose
(7 dragées)	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.

Example 9 (Composition per dragée)

1st Stage	0.030 mg	D-norgestrel
(7 dragées	33.220 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
2nd Stage	0.080 mg	mestranol
(14 dragées)	0.030 mg	D-norgestrel
	33.140 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
3rd Stage	33.250 mg	lactose
(7 dragées)	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.

Example 10 (Composition per dragée)

1st Stage	0.500 mg	norethisterone acetate
(7 dragées)	32.750 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
2nd Stage	0.080 mg	mestranol
(14 dragées)	0.500 mg	cyproterone acetate
	32.670 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
3rd Stage	33.250 mg	lactose
(7 dragées)	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.

Example 11 (Composition per dragée)

1st Stage	0.300 mg	norethisterone
(7 dragées)	32.950 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
2nd Stage	0.080 mg	mestranol
(14 dragées)	0.300 mg	norethisterone
	32.870 mg	lactose
	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.
3rd Stage	33.250 mg	lactose
(7 dragées)	18.000 mg	corn starch
	2.100 mg	polyvinylpyrrolidone
	1.650 mg	talcum
	55.000 mg	total weight which is supplemented with a standard sugar mixture to about 90 mg.

C L A I M S

1. Two-stage contraceptive, comprising in the first stage a gestagen and in the second stage a combination of a gestagen and an estrogen besides the carrier substances, taste corrigents and/or fillers that are commonly used by the galenic pharmacy.

2. Contraceptive as in claim 1, comprising the same gestagen in the first and the second stage.

3. Contraceptive as in claim 1, comprising different gestagens in the first and the second stage.

4. Contraceptive as in claims 1, 2, and 3, comprising in the first stage a gestagen of a quantity corresponding per dosage unit to that of 0.300 to 2.000 mg norethisterone acetate, and in the second stage a combination of a gestagen of a quantity corresponding per dosage unit to that of 0.300 to 2.000 mg norethisterone acetate and an estrogen of a quantity corresponding per dosage unit to that of 0.020 to 0.050 mg 17α-ethinyl estradiol.

5. Contraceptive as in claims 1, 2, 3, and 4, comprising in the first stage a gestagen of a quantity corresponding per dosage unit to that of 0.500 to 0.700 mg norethisterone acetate, and in the second stage a combination of a gestagen of a quantity corresponding per dosage unit to that of 0.500 to 0.700 mg norethisterone acetate and an estrogen of a quantity corresponding per dosage unit to that of 0.020 to 0.050 mg 17α-ethinyl estradiol.

6. Contraceptive as in claims 1-5, comprising norethisterone acetate as the gestagen.

7. Contraceptive as in claims 1, 3, 4, and 5, comprising in the first stage norethisterone acetate as the gestagen and in the second stage cyproterone acetate as the gestagen.

8. Contraceptive as in claims 1-7, comprising 17α-ethinyl estradiol as the estrogen.

9. Pharmaceutical packs, comprising two-stage contraceptives in a certain sequence adapted to the dosage units, characterized in that the first 5 to 8 dosage units contain a gestagen of the quantity corresponding per dosage unit to that of 0.300 to 2.000 mg norethisterone acetate; that the following 12 to 16 dosage units contain a gestagen of the quantity corresponding per dosage unit to that of 0.300 to 2.000 mg norethisterone acetate, and an estrogen of the quantity corresponding per dosage unit to that of 0.020 to 0.050 mg 17α-ethinyl estradiol; and that the last 5 to 8 dosage units contain no gestagen and no estrogen.

10. Pharmaceutical packs comprising two-stage contraceptives according to claims 1-8.

11. Pharmaceutical pack as in claim 10, comprising 5 to 8 dosage units of gestagen of the first stage, 12 to 16 dosage units of the combination of the second stage and, possibly, 5 to 8 gestagen- and estrogenfree dosage units.

12. Pharmaceutical pack as in claims 10 and 11, comprising 7 dosage units of gestagen of the first stage, 14 combination dosage units of the second stage and, possibly, 7 gestagen- and estrogenfree dosage units.